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(56) Documents cited
**GB 2069336 A** **GB 1521505 A** **GB 1412969 A**
**GB 1091660 A** **GB 0998794 A**
**Merck Manual, Edition 14 (1982) p.1669 under "Endometriosis"**
**Extra Pharmacopoeia (Martindale), Edition 29 p.1387, see "Progestagens", pp.1391-2**

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# (54) Progesterone compositions for treating endometriosis

(57) The invention concerns the use of 16-methylene-17α-acetoxy-19-nor-progesterone for the manufacture of a pharmaceutical composition for the treatment of endometriosis and other estrogen-dependent conditions.

GB 2 252 49

# Pharmaceutical Composition

The invention relates to a novel pharmaceutical composition for the treatment of endometriosis and other estrogen-dependent conditions, comprising an effective amount of 16-methylene-17α-acetoxy-16-nor-progesterone (I) and at least one physiologically acceptable carrier or adjuvant.

Endometriosis is one of the most common conditions encountered in gynecology and a major cause of infertility. The disease is characterized by the presence of endometrial tissue outside the uterine cavity. The most common sites of implantation are the ovaries, utero sacral ligaments, rectovaginal septum, sigmoid colon, pelvic peritoneoum and internal surface of the fallopian tubes, where it may cause tubal occlusion.

Endometriosis may be treated by either surgery or long-term administration of anti-gonadotropins which block gonadotropin secretion, inhibit ovulation and as a consequence suppress menstruation. The inhibition of gonadotropin secretion causes a significant reduction in the synthesis of endogenous estrogen, the hormones which stimulate the growth of both normal endometrium and endometriosis tissue. The most effective drugs prescribed for endometriosis today are danazol and gestrinone. Danazol remains the most widely used drug in the treatment of endometriosis. The doses prescribed vary from 200 mg to

severity of the disease. Because of the high doses required, side effects may become intolerable. Weight gain, breast atrophy, hirsutism, hoarseness, arthralgia, acne, seborrhea, oedema, hair loss and chloasma are some of the most common side effects reported.

Gestrinone, in addition to its antigonadotropin effects, interferes with the binding of endogenous estrogen to estrogen receptors, provoking atrophy of both normal endometrium and endometriosis implants. The advantage of gestrinone over danazol is its high potency, which allows control of endometriomata with relatively low doses, 2.5 mg twice or three times weekly. In addition to convenience of administration, treatment with gestrinone provokes less side effects than danazol. However, side effects associated with androgenicity of the drug remain an important drawback of this compound. Seborrhea and acne, for example, develop in most patients.

The latest entry in the armamentarium against endometriosis is the luteinizing hormone releasing hormone (LHRH) analog. This compound disallows gonadotropin secretion and induces a reversible menopause. Although this mechanism of action does suppress ovulation and provokes regression of endometriosis, its acceptance is rendered difficult because of the menopausal consequences which it entails. Hot flushes, dryness of the vagina, sweating, depression and osteoporosis have been reported as major side effects.

Thus, all these known methods of treatment of endometriosis show considerable disadvantages. It is an object of the present invention to provide a novel approach to the treatment of endometriosis (and other estrogen-dependent conditions), which does not have these disadvantages or at least shows them to a smaller extent only.

It has been found that this can be achieved by the use of the known compound I (cf. GB-1,091,660), a dienic steroid devoid of androgenic and estrogenic properties for this purpose, preferably in form of an implant. Attempts to develop I as an oral contraceptive failed either because of poor absorption or rapid inactivation in the gut and liver but it has been partially developed as a longacting contraceptive under the form of a subdermal implant. Multiple subdermal implants were used experimentally as long-acting contraceptives for periods of 8 months to almost 2 years. Other studies indicated that one single implant containing 35 mg of the steroid provides contraceptive protection through ovulation inhibition for as long as 8 months. Treatment with I was remarkably devoid of androgenic side effects such as seborrhea, acne, hirsutism or breast atrophy. For twenty years no use for I implant has been envisaged other than contraception.

Because of its gonadotropin inhibiting effect and its ability to depress estrogen secretion following insertion of one single I implant, women with endometriosis cease to menstruate and are relieved from pain. After a short time following insertion of the implant endometriosis tissue presents regressive changes. As the implant releases I steadily for 6 to 8 months, the patient remains symptomless as the disease regresses. An implant 3.0 to 4.0 cm long should be sufficient to provide protection for 6 to 8 months but in severe cases implants may have to be renewed after six months because treatment must be extended to one year or longer.

The basis for therapy with the I implant is ovulation suppression and inhibition of estrogen peaks which stimulate the growth of endometriomata.

Other estrogen-dependent conditions such as myomas, breast fibrocystic disease etc. can be treated with I in a similar manner.

Another object of the invention is a process for the manufacture of a pharmaceutical composition for the treatment of endometriosis and other estrogen-dependent pathologies which comprises transforming an effective amount of I together with at least one physiologically acceptable carrier or adjuvant into a suitable dosage form, preferably into an implant.

Such implants can be of a resorbable type, e.g. on the base of lactide-glycolide copolymerisates and/or collagen, or of a non-resorbable type, e.g. on the base of silicons such as Silastic®. These latter are preferred and can advantegously be prepared by cutting suitable segments from a tubing, closing one end of the segment, e.g. with medical adhesive, filling the segment with I and closing the other end of the segment.

It is also possible to use other suitable forms of pharmaceutical compositions, such as suspensions, e.g. suspensions comprising micro-particles of lactide-glycolide copolymerisates containing I, furthermore other injectables or patches.

It is possible to use I with or without an adjuvant; it is preferred to use it without adjuvant which simplifies the galenic.

Example: Implants

The implants are prepared by cutting segments of medical grade silastic tubing, presently manufactured by the Dow

or equivalent, with inside diameter of .025 inches and external diamter of .047 inches. Segments should measure from 1-4 cm. Tubing with thinner wall may be used whenever the speed of drug release is to be accelerated and tubing with thicker walls should be used when the release rate is to be reduced in order to prolong duration of the implant life. The second step consists in closing one end of each individual segment with medical adhesive (silicone type A), presently made by Dow Corning, Cat. No. 891. Before the adhesive is applied, the segments of tubing should be thoroughly cleaned and degreased with non-oily soap in hot water and then rinsed with distilled water. An amount of adhesive sufficient to fill of the segment of tubing is applied and left to cure for 24 hours. The following step consists in filling the segment of tubing with I. The drug is packed inside the segment of tubing. Only one millimeter of the tubing remains unfilled, making room for the application of the closing portion of adhesive. After packing the drug, one drop of the adhesive is applied and the capsules thus closed are left to cure for another 24 hours. The capsules can be placed inside plastic envelopes or glass ampoules, which are closed by heat and then heat sterilized in an autoclvae fo 15 minutes or dry heat sterilized for six hours at 160 °C.

Implants may measure from 1 to 4 cm and contain from 1 to 100 mg,more specifically 5 to 50, e.g. either 10, 20, 30 or 40 mg of I.

After insertion subcutaneously, the implant should release the steroid for six months to one year. Its release rate may be prolonged by either adding a saml1 amount (10 to 20 %) of an excipient such as cholesterol or by the use of a less permeable silastic. When cholesterol is added, it is preferably mixed with I filling the segment of tubing.

## Patent Claims

1. A pharmaceutical composition for the treatment of endometriosis and other estrogen-dependent conditions, comprising an effective amount of 16-methylene-17α-acetoxy-19-nor-progesterone and at least one physiologically acceptable carrier or adjuvant.

2. Process for the manufacture of a pharmaceutical composition for the treatment of endometriosis and other estrogen-dependent conditions which comprises transforming an effective amount of 16-methylene-17α-acetoxy-19-nor-progesterone together with at least one physiologically acceptable carrier or adjuvant into a suitable dosage form.

3. 16-Methylene-17α-acetoxy-19-nor-progesterone for the treatment of endometriosis and other estrogen-dependent conditions.

4. Use of 16-methylene-17α-acetoxy-19-nor-progesterone for the manufacture of a pharmaceutical composition for the treatment of endometriosis and other estrogen-dependent conditions.

5. A method of treating endometriosis and other estrogen-dependent conditions which method comprises administering an effective amount of 16-methylene-17α-acetoxy-19-nor-progesterone.

6. A pharmaceutical composition according to Claim 1 which is in form of a single implant.

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**Patents Act 1977**
**Examiner's report to the Comptroller under Section 17 (The Search Report)**

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**Relevant Technical fields**

(i) UK Cl (Edition K ) A5B BHA,BJB,BLF

(ii) Int Cl (Edition 5 ) A61K

Search Examiner

R.B.L. STAGG

**Databases** (see over)

(i) UK Patent Office

(ii)

Date of Search

19 April 1991

Documents considered relevant following a search in respect of claims 1-6

| Category (see over) | Identity of document and relevant passages | Relevant to claim(s) |
|---|---|---|
| X | GB A 2069336 (ROUSELL-UCLA) | 6 |
| Y | GB 1521505 (SCHERING AG) | 2,6 |
| Y | GB 1412969 (SCHERING AG) | 2,6 |
| X | GB 1091660 (MERCK A.G) | 1 |
| Y | GB 998794 (DOW CORNING CORP) | 6 |
| Y | MERCK MANUAL, EDITION 14 (1982) PAGE 1669 UNDER "ENDOMETRIOSIS" | 9 |
| X | EXTRA PHARMACOPOEIA (MARTINDALE), EDITION 29 PAGE 1387 SEE "PROGESTAGENS", PAGE 1391 AND PAGE 1392 | 6 |

| Category | Identity of document and relevant passages | Relevant to claim(s) |
|---|---|---|
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**Categories of documents**

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

A: Document indicating technological background and/or state of the art.

P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family, corresponding document.